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Jubilee Editorial

The medical treatment of angina pectoris

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Fifty years ago, the treatment of angina pectoris made no strong claim for space in journals of cardiology. In January 1939 Maurice Campbell submitted the first article on angina to be published in the *British Heart Journal*,[1] but it was no more than a case report. Five years were to pass before a paper on treatment appeared, written by Wilfred Stokes.[2] He reported an investigation of the value of nicotinic acid in this condition but concluded that the drug did not improve either the prevention or relief of pain. The first and last sentences of the article were similar: both stated that glyceryl trinitrate had no equal in the treatment of angina pectoris—a contention that remained true and mostly unchallenged well into the professional lives of many cardiologists practising today.

The new era of treatment

The therapeutic breakthrough came with the introduction into clinical medicine of β adrenergic blockade: there was no fanfare, but the new class of drugs was recognised as important enough to merit three papers in a single issue of the *Lancet*, one of which included the first account of pronethalol in the treatment of angina.[3] By the time this first clinical agent was found to be unacceptable because of its toxicity[4] others were available to take its place.[5] Despite the obsessive care in drug registration by the Food and Drug Administration that held back progress in the United States for nearly 10 years, β blockade rapidly became an established treatment. When verapamil was introduced, the antianginal effects of this powerful drug were not recognised at first as being the result of a novel type of action. There was, indeed, a celebrated correspondence in the *Lancet*[6] in which notable experts debated whether the efficacy of verapamil was due principally to its actions as a β blocker—by then the passport to respectability. But the calcium channel antagonists have come of age, with a plethora of agents that show more pharmacodynamic diversity than the β adrenergic blockers. We have also acquired sustained action nitrates of proven efficacy, and we have the possibility of widening horizons for intervention together with a bewildering number of drug combinations.

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The introduction of β blockers

The introduction of β adrenergic antagonists owed nothing to serendipity, which is so often the father of progress. During the late 1950s, Black (later Sir James) started his quest for a method of sparing myocardial oxygen demand by attenuating the effects of sympathetic drive on the heart, and led his colleagues in the pharmaceutical industry in the development of analogues of isoprenaline that would block the β receptors,[7] the very existence of which had been postulated only a few years before.[8] He was not the first to produce such a compound: scientists at the Eli Lilly laboratories had already developed dichloroisoprenaline[9] which had become a useful pharmacological tool that first stimulates but then blocks the β receptors. But the clinical potential of β blockade was not seen by the earlier workers. Others, however, were awakening to the value of inhibiting sympathetic influences on the heart. At St Bartholomew's Hospital, sympathectomy was a relatively common treatment for angina during the late 1950s; Hayward and Apthorp were particularly interested in the improvement in effort tolerance that accompanied surgical interruption of the pain fibres. They exercised patients on a treadmill to look for evidence of dangerous ischaemia that might be masked postoperatively. They reported, however, evidence of an improvement in myocardial performance and showed that abnormalities in the electrocardiogram recorded after effort could be abolished or delayed by surgery.[10] As a newly fledged research registrar bereft of a project, after the untimely death of Weitzman in the same department, I decided to

investigate this phenomenon and concluded first that it must be due to interruption of the afferent (motor) sympathetic fibres rather than to pain control, and secondly that it should be possible to reproduce the effect with dichloroisoprenaline or a similar agent. Many months of correspondence with Eli Lilly followed, and a supply of dichloroisoprenaline (with a disclaimer of responsibility) came two days before the publication of the first *Lancet* papers by Black and his colleagues. Only the correspondence and a generous attribution by one of the other early workers who had read the letters[11] remained to sustain my unrealistic pipedream of fame.

Mechanisms of action of β blockers

The mechanisms of action of β blockade in angina are now well known, and can be most easily understood in the context of the concept of the supply and demand of energy for the work of the heart.[12] On the demand side of the equation, heart rate and energy-wasting contractility are reduced, while the reduction in free fatty acid concentration may force myocardial metabolism towards greater dependence on carbohydrate metabolism that is more economical in terms of oxygen use. Wall tension is another factor that may decrease in response to a reduction in blood pressure, but this can be countered by any appreciable dilatation of the heart as a result of β blockade[13] which changes the relation between tension in the ventricular wall and intracavity pressure. On the other side of the equation, the potential for the supply of energy will be favoured by the longer diastolic filling time after β blockade, but perfusion pressure may be augmented less during exercise; the effects on the tone of coronary vessels are contentious and probably variable. Thus not all effects are favourable and individuals vary in the degree to which symptoms improve.

The effect of β blockade on the mortality of angina is unknown and unlikely ever to be tested in a formal clinical trial because the use of a control group deprived of agents of so much symptomatic value has never been appropriate. This is unfortunate because other drugs of comparable efficacy for relief of angina are now available. A few facts may be worth pondering, however, when considering guidelines for treatment: first, the mortality in patients with angina in the United States improved at about the time β blockers were introduced[14]; secondly, one trial in general practice did show an appreciable reduction in mortality in patients on β blockers; however, allocation to the treatment and control groups was not based on an acceptable randomisation procedure[15]; thirdly, protection by some agents has been demonstrated during the convalescent phase after infarction.[16] This is hardly compelling evidence for the contention that β blockers save life in patients with angina, but taken in association with evidence of a protective effect against arrhythmias in animal models[17] and the symptomatic relief they provide, we should continue to regard them as the sheet-anchor of treatment for most patients in the forseeable future.

Calcium antagonists

The introduction of calcium antagonists into clinical medicine also followed research in basic physiology. The concept was pioneered and developed by Fleckenstein *et al.*[18] It now embraces agents of widely different structure and with pharmacological effects both at membrane level (calcium entry blockers) and within cells. The criteria for inclusion of substances as calcium antagonists are not agreed, and the classification in some recent reviews is complex.[19] The drugs of greatest interest in cardiology are the entry blockers that are selective and influence the slow calcium channels of the myocardium and arteries—including the coronary arteries. Their pharmacological activity depends at least in part on limiting the binding of calcium to calmodulin within smooth muscle; calcium calmodulin activates myosin light-chain kinase which phosphorylates myosin, and this in turn promotes contractile activity.[20]

The drugs licensed for use in the United Kingdom have a range of activity: verapamil has the most effect on myocardial contractility and on the activity of the sinus and atrioventricular nodes, while nicardipine has the least direct action on the heart and greatest relative effect on vascular (including coronary) tone. Nifedipine resembles nicardipine and from a clinical viewpoint is similar; diltiazem is near the middle of the spectrum with important actions of both types.

What are the clinical implications of these differences in the actions of calcium channel blockers? In summary, verapamil is a powerful anti-anginal agent that at least matches β blockers in efficacy as a single agent for the treatment of anginal syndromes caused by obstructive coronary disease.[21,22] But it must be used with caution because its negative inotropic effect can precipitate heart failure[23] and its effect on the conducting system can cause sinoatrial block, atrioventricular block, and asystole.[24] Because of the resemblance to the adverse effects of β blockade (mediated by mechanisms that are different yet complementary) the high risk of combination treatment[25,26] should cause no surprise. It can be used successfully, however, in patients with coincident bronchospasm and symp-

tomatic peripheral vascular disease. Towards the other end of the spectrum, nifedipine is a safe drug with unwanted effects that can be very unpleasant[27] yet are reversible and hardly ever life threatening; nicardipine may share this advantage. The special role of these two drugs lies in the prophylaxis of variant or vasospastic angina, but they are not the agents of first choice for the treatment of exertional angina unless others are contraindicated. Unlike verapamil, however, they are useful in combination with β blockers, since reduction in afterload may be of value and many patients with obstructive disease do have symptoms caused by inappropriate coronary tone or spasm.[28] Diltiazem has a broader range of efficacy than other agents because of its more central position on the calcium antagonist spectrum, though it is unlikely to be as effective as verapamil for syndromes that are dominantly obstructive nor as effective as nifedipine or nicardipine for syndromes that are dominantly vasospastic. Its value lies in its therapeutic versatility, its relative safety compared with verapamil, and in the smaller risk of its use in association with β blockers.

The nitrates

Glyceryl trinitrate is the oldest of the present day drugs used to control angina; it was first used to treat migraine.[29] The image of the nitrates has been freshened by the relatively recent demonstration that oral treatment can provide sustained effects,[30 31] by the introduction of new methods of administration,[32-34] and by advances in our knowledge of their mechanism of action. Controversy continues about the value of sustained action in this class of compounds. While this is clearly a desirable therapeutic goal, it carries the risk that efficacy may be negated by the tolerance which develops so readily with nitrates. Short term studies can show impressive persistence of the antianginal effect of isosorbide dinitrate in a range of doses for up to eight hours after dosing,[31] but with long term treatment, with doses four times a day, tolerance does develop and some efficacy is lost.[35] For this reason, some have doubted the value of nitrates in regular drug regimens to control angina and have restricted their use to sublingual preparations for short lived relief.

Recent studies suggest that long acting nitrates are important in prophylaxis. Tolerance occurs particularly in response to the persistence of a threshold concentration of nitrates in the body, and it is greatly mitigated by even brief "nitrate free" periods during the 24 hour day. Thus no tolerance was noted when oral isosorbide dinitrate was given for a month at 8 am and 1 pm.[36] In tests lasting a week, exercise time was improved for only an hour after dosing four times daily but for five hours if doses were restricted to three times a day.[37] For patients with daytime effort angina, Parker has suggested that treatment incorporating the administration of long acting oral nitrates three times a day may be appropriate provided the last dose is taken with an early evening meal rather than at bedtime.[38] The theoretical risk of rebound coronary constriction, similar to that experienced as nitrate concentrations fell in workers with occupational exposure[39] has not become apparent in the clinical evaluation of these agents.

The mechanism of action of nitrates is not yet fully understood but knowledge is unfolding rapidly. They confer benefit in patients with angina with more consistency than any other class of agent, yet their effects on the systemic circulation seem not to be wholly beneficial. In particular the tachycardia induced by nitrates must be unfavourable both in terms of energy demands by the myocardium and the metabolic supply to it. Clinicians must often have been puzzled as they saw the rapid relief of pain despite increasing heart rate in their patients, and sometimes at least must have wondered what unrecognised benefits may be occurring. Appreciation that all was not understood has been reflected in a grumbling controversy on how far relief from angina accrued from systemic effects and how far from effects on the coronary circulation. The pendulum, once firmly on the systemic side, has moved recently to a more central position with the recognition that the pathophysiology of angina forms a continuum with obstructive disease at one end and spasm at the other; the syndrome in most subjects occupies a position somewhere in between. Increased coronary tone may contribute in a recognisable fashion to the pattern of angina,[40] it may increase paradoxically and harmfully as ischaemia develops,[28] and it may account for variation in effort tolerance—as shown for example in the second wind phenomenon.[41] Nitrate induced coronary vasodilatation at the site of this potential increase in tone must complement the systemic effects[28] which have never seemed an adequate explanation for the mechanism of such an effective drug.

At a cellular level the theories that are propounded must take account of the propensity of these drugs to produce tachyphylaxis during continuous administration and a subsequent rapid recovery from this response. Nitrates may work after conversion to nitric acid or nitric oxide which is then converted to nitrosothiols by reacting with the sulphydryl compounds in vascular smooth muscle.[42] These nitrosothiols in turn stimulate guanylate cyclase and increase production of guanosine monophosphate which reduces calcium entry

into the muscle cell. The possible relation with conventional calcium channel blockers is evident, but it should be noted too that nitric oxide has recently been identified as endothelium derived relaxing factor.[43] This factor is present in intact endothelium and can be released by acetyl choline. It is believed to mediate some physiological vasodilatation, and already there is evidence that defects in the mechanism have a role in disease.[44]

In 50 years the wheel has turned full circle and nitrates are once again a focus of interest. No longer the only effective agents as in Stokes's time, they now are central to an attractive unified hypothesis for physiological and pharmacological mechanisms of coronary vasodilatation. Many therapeutic agents must interact with the chain of events extending from nitric oxide and endothelium derived relaxing factor to the calcium entry that controls coronary vasomotor tone. Nitrates, indeed, may resemble opiates in being therapeutic agents of long standing that owe their potency to a chemical relation with substances used in natural control mechanisms.

Other antianginal agents

Some drugs with proven efficacy in angina do not fit easily into the classification comprising nitrates, β blockers, and calcium antagonists. The most notable is perhexiline maleate which was undoubtedly a most useful agent before it was withdrawn by the manufacturers. The most serious unwanted effects occurred particularly in people with defective hepatic hydroxylation,[45] which affects the rate of metabolism of many drugs, but the benefits were impressive in most patients with exercise induced angina. The drug has some calcium channel blocking activity though it has no negative inotropic effect. The antianginal action probably depends on the diversion of myocardial metabolism from fatty acid substrates to the more oxygen-sparing carbohydrates.[46] We lack an alternative agent of this type, and many regret that perhexiline can no longer be used as a secondary drug for patients with refractory angina. Harm is unlikely if plasma concentrations are controlled and an assay is available.[47]

The next 50 years

What of the future? We cannot foretell the path of progress over the next 50 years, but in the foreseeable future we may have agents that will modify more specifically the effects of sympathetic influences on coronary tone perhaps by α blockade, we will certainly have useful adrenoceptor blockers that are partial agonists, a plethora of new calcium antagonists, and perhaps new agents with actions that modify myocardial metabolism. We can be reasonably optimistic that the longer term will bring greater understanding of the pathogenesis of atheroma, the ability to control both its progession and its complications, and ultimately agents to promote its regression. The next jubilee editorial in the *British Heart Journal* on the medical treatment of angina would then be predominantly a historical review.

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